Inherited Risks for Susceptibility to Dental Caries

Charles F. Shuler, D.M.D., Ph.D.

Abstract: Dental caries incidence is affected by host factors that may be related to the structure of dental enamel, immunologic response to cariogenic bacteria, or the composition of saliva. Genetic variation of the host factors may contribute to increased risks for dental caries. This systematic review examined the literature to address the question, “Is the risk for dental decay related to patterns of genetic inheritance?” Numerous reports have described a potential genetic contribution to the risk for dental caries. Studies on twins have provided strong evidence for the role of inheritance. Establishing a basis for a genetic contribution to dental caries will provide a foundation for future studies utilizing the human genome sequence to improve understanding of the disease process. Inherited disorders of tooth development with altered enamel structure increase the incidence of dental caries. Specific genetic linkage has not been determined for all of the syndromes of altered tooth development. Consequently, genetic screens of large populations for genes or mutations associated with increased caries susceptibility have not been done. Altered immune response to the cariogenic bacteria may also increase the incidence of caries. Association between specific patterns of HLA genetic inheritance and dental caries risk is weak and does not provide a predictable basis for predicting future decay rates. The evidence supporting an inherited susceptibility to dental caries is limited. Genetic linkage approaches on well-characterized populations with clearly defined dental caries incidence will be required to further analyze the relationship between inheritance and dental caries.

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The Human Genome Project has achieved its intended goal and recently published the initial complete sequence of the human genome.1,2 This information represents a magnificent resource for further characterizing the genetic contribution to both the etiology of and susceptibility to disease and for developing new strategies for diagnosis, management, and risk assessment. There have been reports that the pattern of host inheritance contributes to either increased susceptibility or resistance to dental caries. Establishing a basis for the genetic contribution to dental caries will provide a foundation for future studies in which the information in the human genome will improve our understanding of the complexity of dental caries pathogenesis.

This review will focus on inherited traits that alter the susceptibility to dental caries in humans. The significant environmental and behavioral contributions to the incidence of dental caries complicate analyses of the role of genetics in dental caries. The genetic contribution is particularly difficult to isolate since there may be primary manifestations directly linked to the disease process and secondary outcomes due to an underlying genetically linked disease.

The literature was searched for evidence of a genetic contribution to caries based on four questions examining inheritance that altered the dental hard tissues, the immune response, the dietary consumption of sugar, or the saliva. The first question examined the role of the dental hard tissues, the target for acid dissolution by cariogenic bacteria, and the genetic contribution of altered enamel biomineralization. The second question searched alterations in the immune response reducing the clearance of the bacteria. The third question evaluated the impact of inherited deficiencies in sugar metabolism that could alter the substrate availability. The fourth question examined the inheritance of parameters related either to either salivary flow or saliva constituents. These four searches provided a broadly based analysis of several inherited properties that have different roles in the multifactorial pathogenesis of dental caries and identified several thousand references containing potentially linked research results.

The literature on the genetic contribution to dental diseases has been reviewed several times in the past forty years.3-12 Genetically regulated processes identified as contributing to caries incidence included tooth eruption and development, salivary flow and saliva components, and tooth morphology. The most convincing data on the role of genetics in the pathogenesis of dental caries has been developed by analyzing the caries incidence in monozygotic and dizygotic twins. The conclusions of Niswander—“the accumulated data sug-
suggest that there are significant genetic factors in caries susceptibility," and "the relative magnitude of genetic effects compared to environmental effects is uncertain"—remain as the field enters the twenty-first century.6

The objectives of this systematic review were: 1) to examine the literature on studies done in humans to identify genetic characteristics linked to either increased or decreased risk for dental caries; 2) to exclude animal studies from the evidence-based reviews; 3) to review the literature for reports linking increased/decreased dental caries incidence with genetic syndromes; and 4) to identify areas of future analysis that might provide greater insight into the genetic contribution to the risks for dental caries.

A Genetic Contribution to Dental Caries Through Twin Studies

Prior to the advent of molecular biology and analysis of the genomic DNA sequence, the study of traits and susceptibilities in twins represented one of the most direct measures of analyzing the contribution of inheritance to disease incidence. Dental caries has been examined in twin populations since early in the twentieth century (Table 1). One of the first studies evaluating twins examined 301 pairs of twins, of which 130 were monozygotic and 171 were dizygotic.13 The evaluation compared the caries incidence of monozygotic twins with same-sex dizygotic (ninety-three pairs) and different-sex dizygotic (seventy-eight pairs) twins. The results demonstrated that monozygotic twins had a more similar caries incidence than dizygotic twins and that different-sex dizygotic twins had the greatest variance. The investigators concluded that the results “suggest that heredity plays a subsidiary part in the incidence of caries.” Goldberg found that identical twins showed decay in corresponding teeth; however, a detailed statistical analysis was not completed.14 These investigators reached the conclusion that “Heredity affects dental decay only in as much as it controls the shape of a tooth and its pits and fissures and its position in the dental arch.” The early twin studies provided some indication that inheritance played a role in caries, but the conclusions were that inheritance was only a contributor to the process.

Twin studies advanced later in the century as techniques to identify monozygotic twins and dizygotic twins were developed. Four studies detected a statistically significant genetic component in the susceptibility to caries and demonstrated that the caries experience of monozygotic twins had a greater concordance than either dizygotic twins or unrelated controls.15-18 Mansbridge examined 224 pairs of twins and concluded that “Environmental factors clearly have greater influence but the genetic factors also contribute to the causation of dental caries.”16 These studies also had sufficient numbers of individuals and tooth surfaces to begin to compare pit and fissure versus smooth surface caries. This led to the conclusion of Finn and Caldwell that “Equal genetic weight should not be ascribed to both types of lesions.”17 The findings were that the DMF difference between monozygotic and dizygotic twins was most dramatic for smooth surface caries on anterior teeth.

Additional twin studies completed in the 1970s further developed the previous line of research.19,20 Bordoni concluded that there is a “strong genetic component in primary teeth which affects the incidence of caries.”19 This association was not further developed, and the genetic contribution to tooth morphology and eruption timing was the major factor. Fairpo similarly concluded that his study “indicates that there is some genetic influence on the susceptibility to caries attack of both deciduous and permanent teeth.”21 In all of the studies, the twins were reared together, so the similar environmental aspects represented a confounding variable in the separation of the full contribution of inheritance to the incidence of dental caries.

A major advance in the understanding of the role of inheritance and the incidence of dental caries was achieved by analyzing twins reared apart who were enrolled in the Minnesota Study of Twins Reared Apart.21,22 These two studies had a major advantage in that the patients had an average age greater than forty and did not share similar environments from shortly after birth until the time of analysis. The analysis demonstrated a highly significant (p<0.001) relationship between the numbers of teeth present and the percentage of teeth/surfaces restored when comparing monozygotic and dizygotic twins reared apart. Bonaas concluded that the study provided “New evidence for a marked genetic component to dentate status and dental caries experience.”21 Boraas also speculated on the particular inherited traits that could contribute to the results by stating “Several genetically variable factors which may be involved in the development of dental caries and could contribute to the greater MZ [monozygotic] similarity in dental caries experience [are] 1) Salivary factors and oral flora, 2) tooth eruption time and sequence, 3) tooth morphology, 4) arch shape, 5) dental spacing, 6) propensity for diet.”22 Conry extended the same study to a greater number of twins and reached the same conclusions; however, he was also unable to determine the
specific genetic factor that contributed to the similarity of caries incidence between the monozygotic twins.22 The analysis of twins raised apart provides the strongest evidence of a genetic contribution to the incidence of dental caries. The similarity in dental caries experience between monozygotic twins reared apart may be either a higher or a lower caries incidence. The analysis of dental caries incidence in monozygotic and dizygotic twins indicates that a large number of different genes contribute to the observed outcomes. Although the twin studies provided strong evidence of a genetic contribution to dental caries risk, none provided any evidence of linkage to specific genes.

## Table 1. Evidence for genetic contribution to the susceptibility to dental caries through analysis of twins

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Controls</th>
<th>Genetic Analysis</th>
<th>Caries Assessment</th>
<th>Data Analysis</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1927</td>
<td>Bachrach &amp; Young</td>
<td>Matched pairs</td>
<td>MZ Twins (130) 3-14 yrs</td>
<td>DZ Twins (171)</td>
<td>Zygosity Testing</td>
<td>DMF, dmf</td>
<td>Correlation MZ and caries 0.67</td>
<td>Heredity a subsidiary part in caries incidence</td>
</tr>
<tr>
<td>1930</td>
<td>Goldberg</td>
<td>Comparative</td>
<td>MZ &amp; DZ Twins 42 pairs</td>
<td></td>
<td>Zygosity Testing</td>
<td>Arch form</td>
<td>Comparison</td>
<td>Heredity affects caries through tooth form</td>
</tr>
<tr>
<td>1958</td>
<td>Horowitz et al.</td>
<td>Matched pairs</td>
<td>MZ Twins (30)</td>
<td>DZ Twins (9)</td>
<td>Zygosity Testing</td>
<td>Caries Experience Ratio</td>
<td>F-Test p&lt;0.001</td>
<td>MZ greater caries concordance</td>
</tr>
<tr>
<td>1959</td>
<td>Goodman et al.</td>
<td>Matched pairs</td>
<td>MZ Twins (19) 19 yrs</td>
<td>DZ Twins (19)</td>
<td>Zygosity Testing</td>
<td>Caries Experience Ratio</td>
<td>F-Test p&lt;0.05</td>
<td>Intrapair variance of DZ greater than MZ</td>
</tr>
<tr>
<td>1959</td>
<td>Mansbridge</td>
<td>Matched pairs</td>
<td>MZ Twins (96) 5-17 yrs Age/Sex/Eruption</td>
<td>DZ (128) Unrelated (112)</td>
<td>Zygosity Testing</td>
<td>DMF, dmf</td>
<td>Chi-square</td>
<td>Genetic contribution less than environment</td>
</tr>
<tr>
<td>1963</td>
<td>Finn and Caldwell</td>
<td>Matched pairs</td>
<td>MZ Twins (35) 7-15 yrs</td>
<td>DZ Twins (31) Unrelated (25)</td>
<td>Zygosity Testing</td>
<td>DMF, dmf</td>
<td>F-Test p&lt;0.0005</td>
<td>Smooth surface caries greater genetic link</td>
</tr>
<tr>
<td>1973</td>
<td>Bordoni et al.</td>
<td>Matched pairs</td>
<td>MZ Twins (17) 4-8.5 yrs</td>
<td>Unrelated (17)</td>
<td>Zygosity Testing</td>
<td>dmf</td>
<td>F-Test p&lt;0.001</td>
<td>Genetic contribution less than environment</td>
</tr>
<tr>
<td>1979</td>
<td>Fairpo</td>
<td>Matched pairs</td>
<td>MZ Twins (100) 5-15 yrs</td>
<td>DZ Twins (120)</td>
<td>Zygosity Testing</td>
<td>DMF, dmf</td>
<td>F-Test p&lt;0.001</td>
<td>Genetic contribution to caries for deciduous &amp; permanent dentitions</td>
</tr>
<tr>
<td>1988</td>
<td>Boraas et al.</td>
<td>Matched pairs</td>
<td>MZ Twins (64) 40 yrs Reared apart</td>
<td>DZ Twins (33) 40 yrs Reared apart</td>
<td>Zygosity Testing</td>
<td>DMFS</td>
<td>2-way ANOVA p&lt;0.001</td>
<td>Marked genetic component to dental caries experience</td>
</tr>
<tr>
<td>1993</td>
<td>Conry et al.</td>
<td>Matched pairs</td>
<td>MZ Twins (46) 40 yrs Reared apart</td>
<td>DZ Twins (22) 40 yrs Reared apart</td>
<td>Zygosity Testing</td>
<td>DMFS</td>
<td>2-way ANOVA p&lt;0.005</td>
<td>Teeth present, surfaces restored and caries attributable to genetic variance</td>
</tr>
</tbody>
</table>

**Genetic Modification of Dental Enamel**

The understanding of the genes that produce the enamel matrix has greatly expanded in the past few years as genome information has been developed. Several investigators have contributed to the cloning of enamel matrix genes, chromosomal localization of the genes, and linkage of genes to human syndromes of altered tooth development.23-30 In each of these analyses, a highly defined clinical phenotype is available to iden-
tify the altered biomineralization matrix protein and to begin to search the genome for linkage to a precise change in DNA sequence. These types of studies provide a model for the approach to genetic linkage that can be used when the clinical phenotype is highly defined.

Numerous reports mention dental caries as a component of a well-defined inherited genetic syndrome with craniofacial phenotypes. These case reports and small sample surveys often document alterations in the morphology of teeth and formation of the enamel as well as the caries experience of the patient. Although this information is available, a correlation with genotype is precluded. These few sample references demonstrate the problems in linking the genetic syndrome, often resulting from a single gene mutation, to the incidence of dental caries. It may be possible in the future to better analyze the genetic contribution to dental caries incidence when the specific genes responsible are more well characterized.

One syndrome with alterations to the dental hard tissues and increased caries susceptibility has been characterized. This syndrome, epidermolysis bullosa (EB), has been shown to have both an alteration in the enamel and an increased caries incidence. The analysis of the EB reports is presented in Table 2. The mutations in EB result in four different forms of the disease: recessive dystrophic; dominant dystrophic; junctionalis; and simplex. Wright examined 252 patients and characterized the caries disease incidence with the specific type of EB. Analysis of the four forms has shown that two of the variants, EB-junctionalis and EB-recessive dystrophic, are associated with an increased incidence of dental caries. The enamel from patients with these two variants has been analyzed for features that might result in the predisposition to dental caries. The junctionalis form has been shown to have altered chemical composition of the enamel, while the recessive dystrophic form does not exhibit altered enamel. Patients affected by EB have multiple associated oral mucosal complications associated with the separation of the mucosa and attendant complications. The evidence is strongest for EB-junctionalis that a primary defect in the enamel secondary to the disease has resulted in the increased dental caries risk. In EB-junctionalis, the enamel has greater porosity and thus increased surface area for the effects of acids generated by cariogenic bacterial, and the enamel contains large amounts of serum albumin that inhibits crystal formation and thus remineralization of altered sites. The genetic origin for EB-junctionalis has been linked to one of three different genes: laminin 5, β4-integrin, and Type XVII collagen. All three of these genes have the potential to alter the relationship of the ameloblast to the developing enamel extracellular matrix and thus lead to a primary defect in the enamel hard tissue. The precise mechanism has not been determined, but EB provides the best evidence for a syndrome-related gene defect directly altering the tooth hard tissue and rendering the tooth more susceptible to dental caries.

Table 2. Evidence for genetic contribution to the susceptibility to dental caries in epidermolysis bullosa

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Controls</th>
<th>Genetic Analysis</th>
<th>Caries &amp; Tooth Assessment</th>
<th>Data Analysis</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Wright</td>
<td>Matched pairs</td>
<td>10 EB Inversa</td>
<td>age/sex</td>
<td>Syndrome criteria</td>
<td>DMFS Oral Exam</td>
<td>Correlation</td>
<td>EB-inversa had increased caries rates but decreased mouth opening as well</td>
</tr>
<tr>
<td>1994</td>
<td>Wright et al.</td>
<td>Comparative</td>
<td>252 EB patients 55-rec dystrophic 39-dorm dystrophic 26-junctional 132-simplex</td>
<td>same group</td>
<td>Syndrome criteria</td>
<td>DMFS Enamel formation</td>
<td>Correlation</td>
<td>EB-J and EB-RD increased carries EB-DD and EB-S no difference from normal in caries incidence</td>
</tr>
<tr>
<td>1996</td>
<td>Kirkham et al.</td>
<td>Comparative</td>
<td>EB-RD patients</td>
<td>Normal teeth</td>
<td>Syndrome criteria</td>
<td>Enamel formation</td>
<td>Correlation</td>
<td>No change in enamel that could be correlated to caries</td>
</tr>
<tr>
<td>2000</td>
<td>Kirkham et al.</td>
<td>Comparative</td>
<td>EB exfoliated &amp; extracted teeth</td>
<td>Normal teeth</td>
<td>EB syndrome Determination</td>
<td>Tooth mineral &amp; albumin content</td>
<td>Observational</td>
<td>EB Junctionalis decreased mineral content, increased albumin and increased caries</td>
</tr>
</tbody>
</table>
Genetic Modification of Immune Response

Individuals with either an inherited or acquired immune deficiency are subject to increased risks for and incidence of dental caries. Animal models of differential caries susceptibility have also been linked to immune complex loci. These observations have led to analyses of specific immune complex molecules for association with increased risks for caries. The analysis of the reports on the linkage of immune complex types with altered enamel development are included in Table 3.

The earliest study was conducted by Lehner et al., who analyzed the distribution of HLA DR antigens in a group of twenty-four individuals with either high or low DMFS indices. In this study it was shown that HLA DRw6-1,2,3 had a significant relationship to the DMFS index and to low dose response to Streptococcu mutans antigens. HLA-DR4 did not demonstrate the same relationship to caries incidence. A similar study was conducted by de Vries on military recruits matched for all criteria other than caries-free and caries-active. The de Vries study did not detect a relationship between the HLA DR types and caries incidence.

Recent studies by Senpuku and Acton have correlated specific HLA DR types with binding S. mutans antigens and S. mutans colonization. Acton concluded that “genes within MHC modulate the level of oral cariogenic organisms”; however, that study of 186 African-American women did not demonstrate a positive correlation between HLA type and DMFS.

Table 3. Evidence for genetic contribution to the susceptibility to dental caries through MHC analysis

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Study Design</th>
<th>Study Population</th>
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<th>Caries &amp; Tooth Assessment</th>
<th>Data Analysis</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>Lehner et al.</td>
<td>Matched groups</td>
<td>Low DMFS (1) 23 yrs old</td>
<td>High DMFS (18)</td>
<td>HLA typing</td>
<td>DMFS</td>
<td>F-test</td>
<td>p&lt;0.0008</td>
</tr>
<tr>
<td>1985</td>
<td>de Vries et al.</td>
<td>Matched pairs</td>
<td>Military recruits caries-free</td>
<td>Military recruits caries-active</td>
<td>HLA-Drw6 on blood cells</td>
<td>DMFS</td>
<td>F-test</td>
<td>No relationship of HLA DRw6 and caries incidence</td>
</tr>
<tr>
<td>1994</td>
<td>Mariani et al.</td>
<td>Independent groups</td>
<td>82 celiac patients</td>
<td>189 normal</td>
<td>Serology for celiac disease</td>
<td>Enamel Defect determination</td>
<td>ANOVA</td>
<td>p&lt;0.005</td>
</tr>
<tr>
<td>1996</td>
<td>Aine</td>
<td>Correlative</td>
<td>Adults &amp; children with celiac disease</td>
<td>Same group</td>
<td>Serology for celiac disease</td>
<td>Enamel Defect determination</td>
<td>Correlation</td>
<td>HLA-DR3, extended haplotype A1,B8 correlated with enamel defects</td>
</tr>
<tr>
<td>1997</td>
<td>Aguirre et al.</td>
<td>Correlative</td>
<td>137 celiac disease patients</td>
<td>Same group</td>
<td>Celiac disease &amp; HLA serology DR7, DR3, DQ2</td>
<td>Enamel Defect determination</td>
<td>Correlation</td>
<td>Celiac disease HLA DR3 increased enamel defects p&lt;0.006, no caries effects</td>
</tr>
<tr>
<td>1998</td>
<td>Senpuku et al.</td>
<td>In vitro</td>
<td>Nine adult donors</td>
<td>HLA Types</td>
<td>Serology for HLA</td>
<td>S. mutans antigen binding to HLA</td>
<td>Observational</td>
<td>S. mutans antigen antigen bound to HLA DR8, DR5 and DR6 most strongly</td>
</tr>
<tr>
<td>1999</td>
<td>Acton et al.</td>
<td>Comparative</td>
<td>186 primiparous African-American women</td>
<td>Same group</td>
<td>HLA typing on blood cells</td>
<td>DMFS and S. mutans antigen binding to HLA</td>
<td>Chi-square Fisher's exact</td>
<td>p&lt;0.005 DRB1-3 &amp; BRB1-4 linked to high levels of S. mutans No correlation to DMFS</td>
</tr>
</tbody>
</table>
Analysis of celiac disease patients has also demonstrated a significant positive correlation between the HLA typing and the presence of enamel defects that predispose to dental caries. Aine and Aguirre have shown that HLA-DR3 is highly associated with the frequency of dental enamel defects in patients with celiac disease.55-57 Mariani had a similar result with HLA-DR3 associated with increased enamel defects and HLA-DR5,7 associated with a reduced frequency of enamel defects.58 Celiac disease patients have an increased incidence of dental caries, and the enamel defects correlated with the disease process may play a specific role.55 The enamel defects in celiac disease, although correlated with the HLA-DR type, have not been attributed to a specific enamel-altering mechanism associated with the disease.

Two different lines of investigation have provided evidence that the genes in the HLA complex are associated with altered enamel development and increased susceptibility to dental caries. The role of these genes in the immune response to cariogenic bacteria represents a mechanism that is based on inherited genetic complements and thus provides the opportunity in the future to study specific allelic variants of these genes as a potential marker for increased dental caries risk.

Inherited Alterations in Sugar Metabolism

There were a very limited number of reports in this area, and the literature was not sufficiently detailed to permit an evidence-based review. Early reports examined the relationship of sugar tasting to dental caries and identified a paradoxical relationship between the sensitivity to taste sugar and the incidence of dental caries.59 Hereditary fructose intolerance is a genetic condition that has a direct relationship to the rationale for the stated question; however, only a limited number of small series studies exist.60,61 In these series there is a statistically significant difference in the caries experience of individuals with hereditary fructose intolerance and non-affected controls, but this is directly related to the absence of cariogenic sugars in the diet. Since ingestion of the cariogenic substrate is the most likely avenue for contribution to the multifactorial process of dental caries, inherited defects in sugar metabolism would most likely alter substrate availability in a manner identical to any other dietary restriction and not by a genetically unique mechanism.

Genetic Regulation of Salivary Gland Function

The fourth search question was based on the observation that xerostomia is associated with dramatically increased rates of dental caries. The topic of saliva and salivary function has been reviewed in detail in another systematic review in the conference, so further discussion of those results have not been included in this paper.62

Summary

The year 2001 has seen the publication of the initial complete human genome sequence from two competing international collaborations.1,2 This resource will permit genetic evaluations that were previously impossible and will dramatically extend the understanding of the genetic contribution to disease etiology and progression. As recently as two decades ago, twin studies provided critical information linking genetics and disease susceptibility. The human genome will provide an unprecedented opportunity to extend these findings. Already the results developed from the human genome sequence have provided evidence that humans have far fewer genes than previously predicted and consequently individual genes may provide multiple proteins, each with a different set of properties. The variation in proteins can contribute to the susceptibility for dental caries if a specific protein or a set of different proteins results in altering the host target, host immune response, or salivary interacting factors. Future examinations will continue to examine the different genes critical to the development of craniofacial structures and the maintenance of intraoral homeostasis. Current evidence supports the linkage of altered dental enamel development with increased susceptibility to dental caries. Increased enamel porosity, decreased mineral content, and the presence of enamel crystal inhibitory proteins all are directly linked to dental caries risk. At the present time these results are limited to defined populations with a recognizable genotype-phenotype relationship. In the future these studies may be extended to individuals without the syndromic phenotype but exhibiting altered susceptibility to dental caries, and allelic variants and protein isoforms will be correlated with genetic susceptibility to dental caries. Current evidence also supports the relationship between immune complex genes and different levels of cariogenic bacteria and enamel
defects. The role of these genes and the functionality of the multiple protein isoforms should provide further information linking specific allelic inheritance and caries susceptibility.

The multifactorial nature of dental caries has limited the opportunity to link patterns of inheritance with susceptibility to dental caries. But the twenty-first century has brought a new resource, the human genome sequence, that will provide new avenues to investigate different components contributing to the risk for dental caries.

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